CASE REPORT

Squamous cell carcinoma of external auditory canal lacking epidermal growth factor receptor protein overexpression, in an elderly Omani with oculocutaneous albinism treated with palliative radiotherapy

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Accepted 18 May 2014

SUMMARY

We report a case of squamous cell carcinoma of external auditory canal in an Omani man with oculocutaneous albinism. The disease mimicked inflammatory process revealing positive cultures for various microorganisms during the course of his illness. He was eventually biopsied to rule out atypical infective process or presence of malignancy. He was staged as T4N0M0 and treated with radical doses of palliative radiation therapy which was very well tolerated and resulted in a complete resolution of disease clinically and a major soft tissue response on radiological imaging. Another unique finding was the absence of epidermal growth factor receptor (EGFR) protein overexpression in the tumour specimen. More than 90% of mucosal squamous cell carcinoma (SCC) involving the head and neck region overexpress the EGFR protein in normal skin patients. SCC is the predominant cutaneous malignancy in albinos, and the presence of EGFR protein overexpression in cutaneous SCC is believed to be 56–58% in normal skin patients. The scientific literature is scarce on reporting incidence of EGFR overexpression in either cutaneous or mucosal SCC in albinos, and it remains to be defined whether being albino is the cause for its absence.

BACKGROUND

Albinism is a genetic disorder characterised by lack of skin pigmentation. Its mode of inheritance is thought to vary, depending on the type. The oculocutaneous type is considered autosomal recessive, and the ocular variant sex linked. Melanin is a photoprotective pigment, protecting the skin from the harmful effects of ultraviolet radiation. Its deficiency predisposes to various degrees of actinic injury to the skin, and skin cancers are a major risk associated with albinism.¹ Frequent overexpression of epidermal growth factor receptor (EGFR) protein is seen in (80–90%) mucosal head and neck squamous cell carcinoma (HNSCC).^{2–3} EGFR is an important therapeutic target^{4–5} and a poor prognostic factor in mucosal HNSCC.⁶ The protein expression of EGFR, SH3GL2 and CDC25A is performed by immunohistochemistry (IHC). EGFR protein expression/overexpression in Albino remains to be explored. We present a case of oculocutaneous albinism in an Omani man, who presented with squamous cell carcinoma of unexposed

skin (external auditory canal) which was EGFR protein non-expressive (EGFR IHC score 0). The patient was treated with palliative radiotherapy leading to a complete clinical and a major radiological regression.

CASE PRESENTATION

The case we report is of an 80-year-old Omani man who developed squamous cell carcinoma in his right external auditory canal, on pre-existing oculo-cutaneous albinism. He has also been known to have essential hypertension well controlled on amlodipine, new onset essential tremors on propranolol and bilateral cataract.

The patient has been regularly visiting the ENT outpatients of Sultan Qaboos University Hospital, Muscat, Sultanate of Oman, since June 2012 with recurrent right ear discharge, which was reported to be bloody and purulent. He also complaint of dizziness and fainting at initial presentation. Ear examination was essentially unremarkable and was therefore managed symptomatically. He continued to show at the ENT clinic with similar reports, until a re-examination in September 2012 revealed meatal stenosis, and the presence of an irregular mass deep in the meatus replacing the posterior meatal area and the tympanic membrane. No mastoid tenderness was noted. Audiogram revealed bilateral hearing loss, right profound and left moderate. Eventually, a necrotic mass with foul-smelling discharge eroded through the right ear canal, mimicking an infective process. He was treated as an infective process for 5 months, with appropriate antibiotics according to culture sensitivity patterns and discharged. A series of microorganisms were isolated during the course of illness including *Streptococcus*, *Staphylococcus aureus*, *Proteus mirabilis* and *Pseudomonas aeruginosa*.

A follow-up examination in November 2012, revealed a hard and thick right pinna with inflamed adjacent tissues. The external auditory meatus was narrow and there was a white flesh-like growth occupying the entire external auditory canal while the tympanic membrane was not visible.

INVESTIGATIONS

A CT scan revealed destructive lesion involving the right mastoid and the middle ear (ossicles were

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To cite: Furrukh M, Mufti T, Hamid RS, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-203226

destroyed, but head of malleus was preserved), extending to the jugular foramen eroding the jugular bulb. The vertical segment of the facial nerve could not be seen separately and the internal jugular vein was compressed. The radiological impression was that of the right parapharyngeal infective process complicating chronic right otomastoiditis.

A new CT scan in 6 November 2012, showed opacification of the right external, middle ear and mastoid air cells with heterogeneous enhancement that was more evident at the epitympanum. Significant bony erosions at the right petrous apex with enhancing soft tissue density were seen extending into the jugular foramina. Bony erosions were also seen in the posterior plate of the right carotid canal and in the posterior aspect of the petrous plate with extension. Multiple multiloculated hypodense collections with rim enhancement were seen in the right parapharyngeal with retropharyngeal space extension and significant obliteration of the normal surrounding fat planes. Soft tissue oedema of the related pharyngeal walls with consequent alteration of the pharyngeal air column at the same level was also seen along with inflammatory changes extending from the mastoid down into the soft neck spaces involving the right pterygopalatine and parapharyngeal spaces (figure 1A–F). The right facial artery was completely surrounded by the inflammatory changes. Multiple cervical lymph nodes measuring less than a centimetre were evident, more on the right side, and the largest measured was 9 mm in the right jugular group.

An incisional biopsy of the tumour showed tissue infiltrated by atypical cells arranged in nests and cords. Individual cells showed atypia and pleomorphism. There were foci of keratinisation (figure 2A). Tumour cells were positive for p63 (figure 2B) confirming the diagnosis of poorly differentiated squamous cell carcinoma. The EGFR stain was performed using IHC which was negative (figure 2C). The patient tumour sample was sent for EGFR protein overexpression to Lab21 in the UK, and IHC revealed an EGFR score of 0. He was subsequently referred to the oncology section of the department of medicine. The patient's TNM stage was T4N0M0. By virtue of the location of the tumour, size and extent of local tissue destruction of vital skull base areas, the patient was not found to be a candidate for

radical surgery and deemed unfit for downsizing chemotherapy because of the patient's poor performance status.

TREATMENT

The patient's case was discussed in a multi-disciplinary team setting. By virtue of having oculocutaneous albinism and poor performance status, it was decided not to consider radical radiation doses or to add cetuximab or concurrent chemotherapy to prevent acute radiation injury. He was referred for palliative radiotherapy to the Royal Hospital, Muscat, where he completed planned dose of palliative radiotherapy (3750 Gy in 14 fractions; using mixed photon beam X6 MV and X15 MV combining external beam and three-dimensional conformal radiotherapy) which was completed on 1 January 2013.

OUTCOME AND FOLLOW-UP

On the follow-up examination in oncology department, the patient was found to have improved performance status to Eastern Cooperative Oncology Group PS 1 with marked subjective improvement in pain and complete clinical resolution of the right ear mass on local examination. Otoscopy was essentially unremarkable and there was no evidence of radiation-induced changes except hearing loss due to previous tumour infiltration and destruction of the ossicles. He was followed with CT imaging on 27 March, 2013, suggesting remarkable improvement and resolution in the size of the mass, with apparent residual minimal thickening in the tumour bed, and reappearance of soft tissue planes and air spaces. Bony changes appeared unchanged. The oncological plan was to follow him and assess him both clinically and radiologically, and consider palliative chemotherapy at first sign of symptomatic or radiological progression. The patient was last seen in July 2013 when he flew to Thailand for subsequent management and remained disease free, until filing of this report as per his family.

DISCUSSION

Oculocutaneous albinism (OCA) is a group of autosomal recessive disorders, caused by disruption in melanin synthesis where the skin appears very pale, hair becomes white and often

Figure 1 CT scans of the head and neck.

Figure 2 (A) H&E section of the tumour. (B) P 63 immunohistochemistry (IHC) stain. (C) Epidermal growth factor receptor (EGFR) stain.

translucent and iris/retina becomes devoid of its pigmentation.⁶ Melanin is synthesised in melanosomes (in melanocytes) from the copper-containing enzyme 'amino acid tyrosine'. Albinism is caused by a metabolic disorder where there is either a defect or a distribution in melanin synthesis. Ocular albinism (OA) type I is an X linked disorder associated with the OA1 gene. Type 1 oculocutaneous albinism (OCA1) is reported in Afro-Americans, native Americans, sub-Saharan Africans, while type-4 in Japan and Korea. OCA1 is characterised by the defect in an enzyme tyrosinase, which converts tyrosine to melanin and has genetic defects in tyrosinase gene (OCA1) on chromosome 11, while OCA2 is a defect of the P gene on chromosome 15. OCA3 and

OCA4 are caused by mutation of the tyrosinase-related protein 1 (Typr1) gene, and the membrane-associated transporter protein gene, respectively.⁷

Patients characteristically have eye signs and symptoms of reduced sharpness, refractive errors, monocular vision, pendular astigmatism, photophobia, reduced visual acuity, strabismus due to foveal hypoplasia, optic nerve hypoplasia due to underdevelopment, iris transillumination defects and abnormal decussation of the optic nerve fibres.⁸ These ocular manifestations are almost always present in both forms of albinism; however, the degree of their presentation can vary depending on the type and the racial background of the patient.

Lack of melanin in the skin makes it highly sensitive to actinic damage (UV light exposure), and these individuals are therefore highly susceptible to various skin cancers, including squamous cell carcinoma, basal cell carcinoma and amelanocytic malignant melanoma of the head and neck. The majority of cutaneous squamous cell carcinoma (SCC) (80–90%) arise in the sun-exposed areas of the head and neck in normal individuals.¹ Other hereditary disorders that may make the skin susceptible to SCC include xeroderma pigmentosa, Fanconi's anaemia, Muir-Torre syndrome, epidermodysplasia verruciformis etc.¹ Some common premalignant conditions that may be the harbinger of malignant transformation include Bowen's disease, actinic keratosis, dysplastic nevi, cutaneous horns and moles etc.

Our patient was unique as he developed SCC of the external auditory canal, a part of the body which is not directly exposed to the sun. In addition, the patient's cancer did not express the epidermal growth factor receptor (EGFR) protein on immunohistochemical analysis. EGFR is a transmembrane glycoprotein expressed in various epithelial malignancies for example, adenocarcinoma of the lung, colorectal carcinoma as well as HNSCC). Elevated EGFR mRNA is found in 92% of mucosal SCC tumours,³ and the EGFR levels are increased in poorly differentiated tumours and advanced-stage tumours.⁹ EGFR is a molecular marker for targeted therapy using cetuximab concurrent with radiation therapy. The prevalence of EGFR expression in albino remains to be explored. A high expression of EGFR protein in mucosal SCC is associated with worse prognosis and decreased disease-free survival (DFS).³ A meta-analysis was conducted on the prognostic value of EGFR expression for overall survival (OS) and DFS involving mucosal HNSCC. Thirty-seven studies were included. Overall, EGFR overexpression was associated with shortened OS, but not DFS.¹⁰

EGFR was found to be overexpressed in 46% of cutaneous SCC specimen in a small study, and 56% of primary tumours and 58% of regional metastatic nodal disease in another study. In this study cutaneous SCC was found to have no significant correlation between EGFR expression and survival, locoregional metastasis and time to recurrence. Overall survival did not correlate with EGFR ($p=0.47$) expression in primary lesions nor was it associated with an increase in regional ($p=0.74$) or distant metastasis ($p=0.56$).¹¹

Our patient had extensive local spread and was not found to be a candidate for radical surgery, while the primarily poor performance status at initial presentation, and advancing age limited any attempts of downsizing poly-chemotherapy. The treatment of early skin cancer is radical surgery with negative margins ensuring cosmetic preservation. Little is known about the effects of curative radiation in albinos, as this may potentially cause severe skin injury as a short-term effect including radiation burns, and possibly skin cancers and other late sequelae over longer follow-up. A follow-up response evaluation CT imaging is consistent with a major soft tissue radiological

regression but unchanged bone changes, which are difficult to comment on, whether these are tumour induced or radiation induced.

Learning points

- ▶ Squamous cell carcinoma is the most common skin cancer seen with oculocutaneous albinism.
- ▶ Occurrence of sun unexposed cancer involving external auditory canal remains rare.
- ▶ Furthermore, more than 50% of head and neck cutaneous squamous cell carcinomas are by large epidermal growth factor receptor (EGFR) overexpressing on immunohistochemistry, but our case is negative.
- ▶ The disease mimicked an inflammatory process delaying definitive diagnosis and a chance of radical therapeutic intervention was lost with symptomatic and performance status deterioration of our patient.
- ▶ Radiotherapy is well tolerated at the dose mentioned, without increase in acute sequelae and with equally effective local control and may be considered in albinos.
- ▶ It is worthwhile to examine albino skin for expression of EGFR protein.
- ▶ An earlier biopsy and possibly an earlier discussion in multidisciplinary team setting is mandatory.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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